HUMAN ENDOCANNABINOID SYSTEM EMULATOR

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INTRODUCTION

Action potentials (AP) are electrochemical events that travel along a neuron from its dendrites (inputs), across the cell body, down the axon, to the synapses (outputs) [1]. An AP crosses the synaptic cleft between neurons in the presynaptic-to-postsynaptic direction, following neurotransmitter release by the upstream cell and depolarization of the downstream cell [2]. This process is associated with transmission of information in neural tissues. After action potential initiation, ions such as Ca^{++}, Na^{+} and K^{+} pass through gated pores in nerve cell membranes, causing various short-term and long-term changes to take place, including memory.

Recently, the capability of postsynaptic nerve cells to send signals in the opposite direction, without the use of APs, has been discovered [3]. Two chemicals in the endocannabinoid family so far have been shown to participate in this function; arachidonoyl ethanolamide (anandamide or AEA) and 2-arachidonoyl glycerol (2-AG). Endocannabinoids are chemicals synthesized in the brain which are related to compounds produced by the hemp plant, *Cannabis sativa*.

Retrograde signaling by postsynaptic nerve cells is possible because presynaptic cells have receptors for endocannabinoid compounds: CB1 (central) and CB2 (peripheral). These are "G-protein coupled" family receptors. Unlike most neurotransmitters, the endocannabinoids are not prepackaged within nerve cells for release into the synaptic cleft following an AP. Instead, these arachidonic acid derivatives are synthesized "on-demand" in the postsynaptic neuron as a result of ongoing electrochemical stimulation. AEA, for example, is produced and released into the synapse where it activates CB1 receptors. This temporarily decreases the amount of presynaptic neurotransmitter molecules released. If a stimulatory neurotransmitter is involved (i.e.: glutamate), the postsynaptic neuron's excitability will be decreased; if an inhibitory neurotransmitter is involved (i.e.: GABA), the postsynaptic neuron's excitability will be increased. This allows a postsynaptic neuron to adjust the incoming AP data streams to which it must respond [4].

Retrograde signaling is involved in synaptic plasticity, long term potentiation, and memory.

COMPUTER EMULATION OF NEURONS

The author has previously developed computer emulators, some with custom hardware acceleration, for general human nervous system function [5]; childhood growth and development, mental disorders, and neurologic diseases [6]; hormonal responses [7]; drug effects [8]; the fear response [9]; and trust-love mechanisms [10]. This emulator series is extended here to include simulated retrograde signaling via the endocannabinoid system. This is accomplished using both software and hardware techniques. The emulator operates at several levels: from simulated membrane receptor binding to high-level behavioral effects.

Two years ago at CMBEC the author presented an advanced artificial neuron (AN) he designed using a Texas Instruments MSP430FG439 mixed-signal microcontroller [11]. This micropower (300 µA at 1 MHz, 2.2 V), 16-bit Flash CPU has a rich set of analog components on-chip: 3 operational amplifiers (op-amps), an analog comparator, a 12-bit 12-channel analog-to-digital (A/D) converter and two 12-bit digital-to-analog converters (D/A) [12]. This processor also has abundant digital components as well: 2 KBytes RAM, 60 KBytes Flash ROM, serial and parallel ports and a DMA controller. The author's AN was configured as a pulse-integrating neuron, which could "read" incoming APs from living cells and output AP pulses which would be recognized by living neurons.

This AN is extended for CMBEC 2008 by adding a simulated endocannabinoid system retrograde signaling capability. The block diagram for this AN is given in Figure 1 (following page). There are many similarities with the 2006 neuron design. For example, incoming excitatory and inhibitory AP pulses are summed on a capacitor (labeled "cap") by an op-amp integrator; the resulting output voltage from the integrator goes into an analog comparator for measurement. The threshold trip voltage ("V ref") for this comparator comes from one of four sources under program control. The comparator output is read by an internal digital port which leads to the incoming AP analysis program logic.

A calculated AP output is generated by a MSP430 D/A converter ("DAC 0"), which receives its waveform information from a table of values in Flash, stepped

through sequentially, as a response to incoming APs.

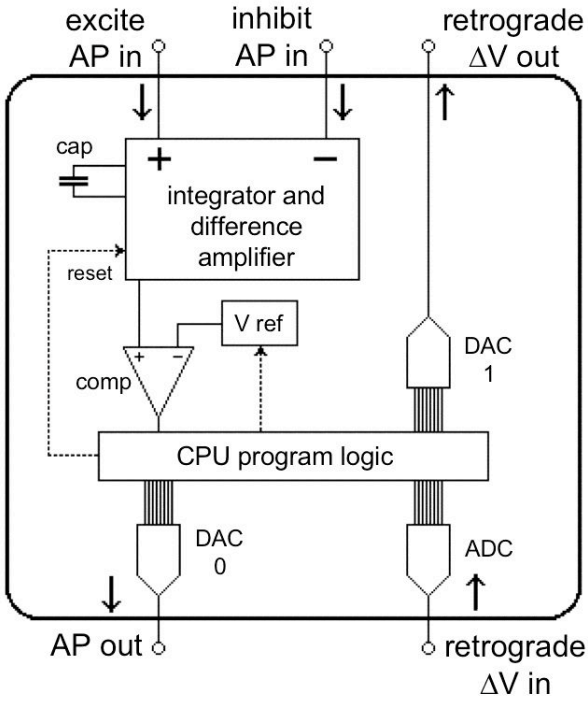

Figure 1: Artificial neuron, 2008 version.

This AP output may consist of a single pulse, or a train of pulses as depicted in Figure 2.

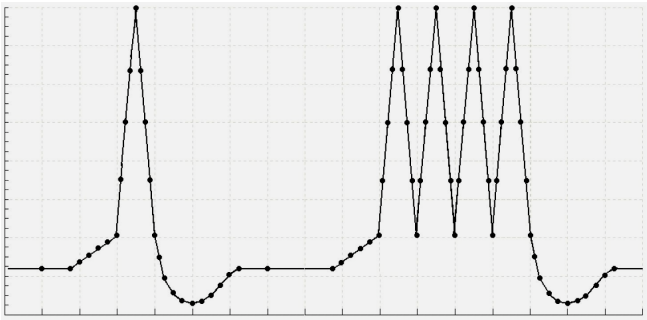

Figure 2: D/A synthesized AP waveforms
(y axis = binary inputs 0-255 to DAC; x axis = milliseconds)

In order to simulate retrograde signaling, the postsynaptic AN D/A converter ("DAC 1") generates a variable voltage which is read by the A/D converter in the presynaptic AN ("ADC"). The literature has little detailed information regarding the endocannabinoid neurotransmitter secretory response induced by incoming APs, so the author devised a "best guess" response curve based on knowledge that on-demand production of AEA by the postsynaptic neuron will be orders of magnitude slower than the release of the usual prepackaged neurotransmitters in presynaptic neurons (Figure 3). This curve has a relatively rapid up-ramp since incoming APs cause AEA to be synthesized and released into the synaptic cleft; there is a long decay portion of the curve as AEA is metabolized and not replaced, if insufficient incoming APs fail to re-stimulate endocannabinoid production. Note that re-stimulation is depicted twice in the Figure, showing elevation of the curve during the decay cycle. This endocannabinoid production response curve is stored in another table of values in Flash ROM.

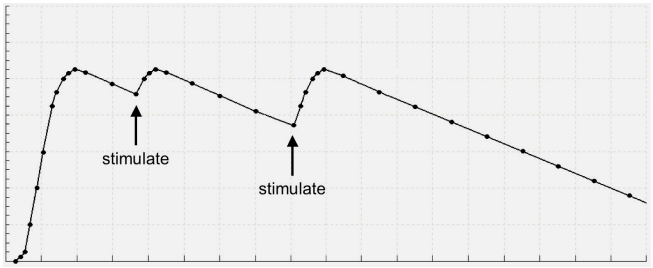

Figure 3: Endocannabinoid neurotransmitter synthesis
(y axis = binary table values 0-223; x axis = seconds)

In operation, the presynaptic AN continually reads the retrograde signaling voltage produced by the postsynaptic AN. As this voltage rises from baseline, the presynaptic AN uses this information to modify the rate and number of APs it outputs to the postsynaptic AN. Thus, the stimulation which the former provides to the latter is controlled (to an extent) by the response of the latter.

HIGH LEVEL EMULATOR RESPONSES

Eventually, a "terminal" postsynaptic AN will be reached; i.e.: one able to trigger the firing of a schema script. A *schema* is an artificial intelligence (AI) device which shares some AN features (i.e.: input recognition) and some knowledge base features (viz.: procedural *action scripts*) [13]. For example, when the simulated adrenaline levels increase, a fight-or-flight response decision is made by the relevant schema (based on the internal hormone level and on external factors such as the threat severity, whether the individual has an escape route, and the presence of weapons). Either the "fight" script or the "flight" script is activated. The success of either script is continuously re-evaluated. At any point the scripted action in progress may be aborted by the schema (i.e.: "flight" is deselected when the previous escape route becomes blocked, and "fight" is then selected instead).

High-level AI (behavioral) schemas are affected by system variables representing the personality of the entity (such as bravery, curiosity, strength, agility, etc), complexity of the knowledge base, memory of recent events, and special missions or goals. These features

are carryovers of the previous robot control system (RCS) upon which the emulator technology is based.

DISCUSSION

This endocannabinoid retrograde signaling system emulator works as described above. Multiple variables are present which allow users to adjust the responses of the simulated neurons at both the presynaptic and postsynaptic levels, for AP and retrograde signaling data. Output AP waveform table-of-values information and the endocannabinoid response curve is also user-configurable. Other system variables and the progress of script execution may be examined in real-time.

The retrograde signaling depicted in this AN uses an analog voltage generated by a D/A converter in the postsynaptic neuron, which is read by an A/D converter in the presynaptic neuron. Nevertheless, the TI MSP430FG439 chip can perform this signaling in other ways: using its serial communications ports, parallel communications ports, or pulse-width modulation. The author favors using analog techniques where possible, as these can be rapidly and easily tested using an oscilloscope and voltmeter.

It is interesting to note that Texas Instruments has recently created an experimental ultra-low voltage version of its MSP430 microcontroller with the help of engineers at MIT [14]. This new chip, described at the *International Solid State Circuits Conference*, February 5, reduces the already-low power consumption of the controller by a factor of ten. Many sections of this mixed-signal microcontroller will operate at just 0.3 volts. The TI and MIT engineers believe that these processors will be especially useful for medical implants, even harvesting their operating power from "ambient energy" (i.e.: via piezoelectric generators or biological fuel cells) in a patient's body.

CONCLUSION

Although this simulated endocannabinoid system retrograde signaling capability works in the laboratory, it is unlikely to be useful directly interfaced to living neurons. This is because the retrograde system is chemical, not electrochemical, and no reversed-APs are generated or read by living tissue. Thus the postsynaptic AN has no simple way to communicate with (and thus, influence) its presynaptic counterpart. Perhaps an electronically-controllable AP-inhibiting chemical release system will be invented in the future (a worthy MEMS-nanotechnology goal). If so, then this simulated endocannabinoid retrograde signaling system would become fully functional with living neural tissue.

REFERENCES

[1] A.L. Hodgkin and A.F. Huxley, "Currents carried by sodium and potassium ions through the membrane of the giant axon of Loligo," *J Physiol*, 116(4), pg.449-472, Apr. 1952.

[2] S. Hormuzdi, M. Filippov, G. Mitropoulou, H. Monyer, R. Bruzzone. "Electrical synapses: a dynamic signaling system that shapes the activity of neuronal networks," *Biochim Biophys Acta*, 1662(1-2): pg.113-137, Mar 2004.

[3] R.A. Nicoll, and B.E. Alger, "The brain's own marijuana," *Scientific American*, 291, pg.70–75, Dec. 2004.

[4] F. Grotenhermen, "Cannabinoids," *Curr Drug Targets CNS Neurol Disord*, 4(5), pg.507-530, Oct. 2005.

[5] P. Frenger, "Human nervous system function emulator," *Biomed Sci Instrum*, 36, pg.289-294, 2000.

[6] P. Frenger, "Forth and AI revisited: BRAIN.FORTH," *ACM Sigplan Notices*, pg.11-16, Dec. 2004.

[7] P. Frenger, "Human hormone function emulator," *Biomed Sci Instrum*, 42, pg.513-517, 2006.

[8] P. Frenger, "Human narcotic use emulator," *Biomed Sci Instrum*, 43, pg.278-283, 2007.

[9] P. Frenger, "Human fear mechanism emulator," *accepted to Biomed Sci Instrum*, 44, 2008.

[10] P. Frenger, "Human trust-love mechanism emulator," *Houston Soc Engr Med Biol Abstracts*, 25, pg.42, 2008.

[11] P. Frenger, ""Creating a Perfect Artificial Neuron," *Can Med Biol Engr Conf*, SC-8.6, pg.1-3, 2006.

[12] Texas Instruments MSP430FG439 Datasheet. Available: http://focus.ti.com/docs/prod/folders/print/msp430fg438.html.

[13] G. Drescher, *Made-Up Minds*, MIT Press, Cambridge MA, 1991.

[14] R.C. Johnson, "TI, MIT team to design ultra-low voltage chip", *EE Times*, Feb. 5, 2008.